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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1560261> since 2016-06-01T11:55:18Z

Published version:

DOI:10.1038/bmt.2016.79

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UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Questa è la versione dell'autore dell'opera:

[Expert Rev Hematol. 2016 Apr 18:1-12.]

ovvero [Martino M1, Lemoli RM2, Girmenia C3, Castagna L4, Bruno B5, Cavallo F5, Offidani M6, Scortechini I6, Montanari M6, Milone G7, Postacchini L8, Olivieri A6.]

The definitive version is available at:

La versione definitiva è disponibile alla URL:

[<http://www.nature.com.offcampus.dam.unito.it/bmt/journal/vaop/ncurrent/full/bmt201679a.html>]

Italian consensus conference for the outpatient autologous stem cell transplantation management in multiple myeloma

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Abstract

Multiple myeloma (MM) is the leading indication for autologous stem cell transplantation (ASCT) worldwide. The safety and efficacy of reducing hospital stay for MM patients undergoing ASCT have been widely explored, and different outpatient models have been proposed. However, there is no agreement on the criteria for selecting patients eligible for this strategy as well as the standards for their clinical management. On the basis of this rationale, the Italian Group for Stem Cell Transplantation (GITMO) endorsed a project to develop guidelines for the management of outpatient ASCT in MM, using evidence-based knowledge and consensus-formation techniques. An expert panel convened to discuss the currently available data on the practice of outpatient ASCT management and formulated recommendations according to the supporting evidence. Evidence gaps were filled with consensus-based statements. Three main topics were addressed: (1) the identification of criteria for selecting MM patients eligible for outpatient ASCT management; (2) the definition of standard procedures for performing outpatient ASCT (model, supportive care and monitoring during the aplastic phase); (3) the definition of the standard criteria and procedures for re-hospitalization during the aplastic phase at home. Herein, we report the summary and the results of the discussion and the consensus.

Introduction

Multiple myeloma (MM) remains the leading indication for high-dose chemotherapy and autologous stem cell transplantation (ASCT) worldwide^{1, 2} and the International Guidelines recommend that ASCT should be offered at some point during the treatment program for a medically fit patient.^{3, 4}

High-dose melphalan (HDM) at 200 mg/m² is the standard conditioning for ASCT^{5, 6} and, today, the treatment should be considered a safe procedure with a very low transplant-related mortality (TRM).^{7, 8, 9} The significant increase in the waiting lists generated concerns about the appropriate use of health care resources and, over the past years, some studies have investigated the safety,

efficacy and potential cost advantages of reducing hospital stay for patients undergoing ASCT.^{10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27}

The ease of administering HDM, the relatively low extra-hematological toxicity and the short period of neutropenia^{5, 6} make MM patients ideal candidates for outpatient ASCT programs. Standardization of criteria for the outpatient ASCT policy is a relevant goal of the Italian hematology and transplant community and may facilitate comparison of retrospective and prospective data. The Italian Group for Stem Cell Transplantation (GITMO) endorsed a panel of 10 experts in the transplant field (MMa, RML, CG, LC, BB, MO, IL, MMo, GM and AO) to propose a consensus for the selection criteria and management of MM patients for ASCT procedure in the outpatient setting.

Methods

A working group of 10 experts from 7 GITMO centers, with specific expertise in the field of ASCT, convened four times to:

- (a) identify common criteria for selecting MM patients eligible for outpatient ASCT;
- (b) define standard procedures for the ASCT outpatient including the ASCT outpatient model, supportive care and monitoring during the aplastic phase;
- (c) define standard criteria and procedures for re-hospitalization.

The panel first met on February 2013 and agreed to adopt a nominal group technique to address the above-reported issues. Before each meeting, the moderator (AO) asked experts to propose statements for each relevant item. The statements were posted by e-mail and discussed in a round-robin fashion during the meetings. The discussion was facilitated by a moderator who invited each expert to express his or her opinion. Voting could be requested when the panel did not reach a consensus. The majority rule was adopted in the case of discordance.

An expert methodologist (LP) and an experienced researcher in the field of MM (FC) supported the research and the final version of the consensus. An expert in the management of infections in neutropenic patients (CG) was also involved.

Systematic review of the literature

An independent librarian carried out a sensitive search in different electronic databases (MedLine, the Cochrane Library (CENTRAL)) to select original research articles on modalities and clinical outcomes of outpatient ASCT in MM. A comprehensive list of terms was tested across databases. Related articles were explored, and a manual search was also performed from retrieved studies. The panel experts were asked to report any article possibly missed. Trial registries (for example, clinicaltrials.gov) were searched for non-published studies in progress. Two investigators read all abstracts. Selected articles had to fulfill the following inclusion criteria: (1) clinical observational or experimental study design, (2) inclusion of at least two patients with ASCT. A full paper was obtained from all the eligible studies and evidence tables were generated.

Quality assessment

Randomized controlled trials were evaluated through the validated quality scale suggested by Jadad *et al.*²⁸ The expert panel agreed to focus on the main issues linked to background questions and main operative questions (Table 1). After a detailed evaluation of the main trials in this field

(Tables 2 and 3), 42 specific questions to be addressed separately by each member of the panel were identified (see Supplementary File). For each question, a minimum agreement of 80% was required, and disagreements were resolved by discussion. The panel formulated the final statements and the key recommendations in a plenary GITMO session (September 2014) (Table 4). The final manuscript was updated, reviewed and approved by the panel in July 2015.

Table 1. Major issues addressed by the expert panel for the outpatient ASCT management in MM patients

Background questions	
1	What is the standard conditioning for MM patients aged < 66 years and candidate for the outpatient ASCT management?
2	Is the ASCT outpatient model safe as the conventional ASCT model in MM patients?
3	What is the preferred model for the ASCT outpatient management in MM patients?
4	Can we make a comparison between the costs and the quality of life for traditional (inpatient) and outpatient ASCT in MM patients?
Operative questions	
1	How to select an MM patient candidate for the outpatients ASCT?
2	Which kind of supportive strategy for the outpatients ASCT?
3	What are the re-admission criteria in the hospital and how to manage those patients who develop relevant complications after outpatient ASCT?
4	How to optimize the performance of the ASCT outpatient in MM?

Abbreviations: ASCT=autologous stem cell transplantation; MM=multiple myeloma.

Table 2. Retrospective clinical studies focused on the evaluation of management and outcome of outpatient ASCT in MM

Author	Year	Specific eligibility criteria	Regimen	Model	No. of transplants	No. of re-admission %	Reasons for hospitalization	TRM %	Comments
Morabito	2002	Psychosocial evaluation to establish skills and compliance of patients and caregivers. Availability of a caregiver on a 24-h basis. Housing near the transplant center. Competency and commitment of patients and caregivers, judged by an educational session	HDM	MIOM	60	56.7	Continuous fluid replacement or slow response to first line antibiotic therapy	0	Patients were admitted for HPC infusion for 2 days for reimbursement purposes. Mucositis was the only independent predictor of break-through fever
Kassar	2007	Patients with a PCP	HDM	TOM	90	58	Fever: 33% No PCP: 13% Mucositis: 6% Other: 6%	0	Eighty percent of the patients remained neutropenic for 5 days or less, and no patient had a neutropenic period longer than 7 days
Holbro	2013	Availability of a caregiver, and residence close to the hospital or acceptance to stay at an accommodation close to the hospital	HDM	TOM	91	84	Fever: 85% Mucositis: 6% Other: 9%	0	The cost savings was \$19,522 (Canadian dollars) per patient compared with inpatient ASCT
Martino	2014	Caregiver on a 24-h basis; housing within easy reach to the transplantation center; adequate activities of daily living, such as eating, cleaning, personal hygiene and ambulation possible independently or under the supervision of a caregiver	HDM	EDM	522	18.8	Fever: 14.6% Mucositis: 1.7% Diarrhea: 1.7% Arrhythmia: 0.4% TIA: 0.2% Cutaneous hemorrhage: 0.2%	1	No center effect was observed. This strategy could be extended to other transplantation centers if a stringent patient selection and appropriate management are applied.
Paul	2015	Availability of caregivers at home; distance to transplant center; patient and physician Preference; performance status of ≤ 1	HDM	EDM	82	67	Fever: 87% Inability to maintain hydration: 7% Other: 65%	0	Carefully selected patients can be managed with a brief initial hospitalization and outpatient follow-up, with low morbidity and mortality

Abbreviations: ASCT=autologous stem cell transplantation; EDM=early discharge model (see Figure 1 for details); HDM=high-dose melphalan; HPC=hemopoietic progenitor cell; MIOM=mixed inpatient-outpatient model (see Figure 1 for details); MM=multiple myeloma; PCP=primary care provider; TIA=transit ischemic attack; TOM=total outpatient model (see Figure 1 for details).

Table 3. Prospective clinical studies focused on the evaluation of management and outcome of outpatient ASCT in MM

Author	Year	Study design	Specific eligibility criteria	Regimen	Model	No. of transplants	No. of re-admission %	Reasons for hospitalization	TRM %	Comments
Jagannath	1997	Prospective non-randomized study	Motivation for self-care, accompaniment by a responsible adult	HDM	TOM	118	21	Fever: 36% Mucositis: 28% Bacteremia or Pneumonia: 28% Other: 6%	0	Total adjusted average charges were \$13 172 lower for outpatients than for inpatients. Outpatient savings were realized mainly through lower hospitalization costs (50% of overall savings).
Gertz	2008	Prospective non-randomized study	All patients are requested to have a chaperone or caregiver with them	HDM	TOM	716	39	Dedining performance status, mucositis infection with hemodynamic instability	1.1	Younger patients and those with serum creatinine levels less than 1.5 mg/dL were more likely to complete the transplant program as outpatients.
Ferrara	2011	The authors compared results between patients receiving either conventional G-CSF or PEG.	Presence of a caregiver, patient's adherence and living within 45-min traveling distance from the hospital	HDM	EDM	PEG: 48 G-CSF: 113	PEG: 12 G-CSF: 26	Febrile neutropenia and mucositis	0 0.8	The administration of single-dose PEG-Filgrastim resulted in no different outcome regarding safety and efficacy as compared with daily G-CSF
Martino	2015	Three-arm prospective, non-randomized study	A caregiver who was willing to stay at home and help, and approval of the home by the medical staff of the bone marrow transplant unit	HDM	HC/ EDOM/ IN	HC = 15 EDOM = 25 IN = 40	HC = 13 EDOM = 8	Fever: 100%	0 0 0	Hospital at home is an alternative to reduce outpatient hospital admissions

Abbreviations: ASCT=autologous stem cell transplantation; EDM=early discharge model (see Figure 1 for details); EDOM=early-discharge outpatient model; HC=home care (see Figure 1 for details); HDM=high-dose melphalan; IN=inpatient; MM=multiple myeloma; PEG=PEGylated G-CSF; TOM=total outpatient model (see Figure 1 for details).

Background questions

What is the standard conditioning for MM patients <66-year-old candidates for outpatient ASCT?

The expert panel agreed to focus on MM patients younger than 66 years, mainly because this homogeneous setting makes acceptable the outpatient ASCT management in the context of a standard conditioning regimen including HDM at 200 mg/m² (Table 1). For patients older than 66 years there is no full agreement on the intensity of HDM, ranging from 100 to 140 mg/m².^{29, 30, 31, 32, 33, 34, 35} As recently reviewed, the standard conditioning for younger patients is still HDM at 200 mg/m², and there is not any evidence that the addition of other agents may improve clinical outcomes.^{5, 6} Elderly patients may not be good candidates for outpatient ASCT due to their reduced medical fitness and presence of comorbidities.¹⁰

Is the ASCT outpatient model safe as the conventional inpatient ASCT model in MM patients?

Reported early morbidity and early mortality rates (TRM at day +100) after conventional inpatient ASCT in younger patients were evaluated. Hematological and extra-hematological toxicities and TRM were compared with those reported in studies on outpatient ASCT models in MM.

MM patients who received myeloablative regimens followed by ASCT developed severe hematological toxicity and duration of aplasia was strictly associated with the amount of CD34+ cells infused. A dose greater than or equal to 2×10^6 CD34+ cells/kg body weight is characterized by a rapid neutrophil (PMN) recovery in most patients.³⁶ No significant advantage has been reported with a CD34+ cell dose higher than 2×10^6 CD34+ cells/kg regarding PMN recovery while a significantly slower platelet recovery has been observed when compared with doses higher than 5×10^6 CD34+ cells/kg.^{36, 37, 38, 39, 40, 41}

According to the current literature,^{42, 43, 44} expert panel agreed to define a graft content of greater than or equal to 2×10^6 CD34+ cells/kg as the standard minimal dose. Moreover, a higher number of CD34+ cells (for example, $3-5 \times 10^6$ /kg) was considered the ideal to minimize the risk of delayed engraftment.

The following end points for hematological toxicity were selected: (1) days of severe neutropenia; (2) requirement of transfusion support; (3) days to PMN and platelet engraftment defined as the second consecutive day with PMN $>500/\text{mmc}$ and platelet $>20\,000/\text{mmc}$, without transfusion support for greater than or equal to 3 days.

As for extra-hematological toxicity, the following end points were selected: (1) incidence of neutropenic fever $>38^\circ\text{C}$ (NF); (2) days of NF; (3) days of IV antibiotics; (4) incidence of documented severe infections; (5) incidence of severe (grade 3–4 according to WHO definitions) mucositis; (6) incidence of major bleedings.

The expert panel agreed that, besides NF, mucositis represents the most frequent complication, although its incidence after HDM was extensively reported in a few reports.^{20, 22, 26}

Recent meta-analyses evaluated early TRM in the main randomized studies in MM, which compared ASCT with chemotherapy, and single versus tandem ASCT. TRM was 3%, slightly higher after the second ASCT.^{45, 46, 47} In a recent large prospective trial, a TRM between 1 and 3% was reported.⁴⁸ In a US study, early TRM was 2% in the 1995–1999 cohort, 2% in the 2000–2004 cohort and 1% in the 2005–2010 cohort.⁹ Our recent national survey in 522 procedures, performed on an outpatient basis, showed an early TRM of 1%.²⁶ Similar data were reported by Gertz et al.²⁰ and Helbro et al.²²

Which is the preferred model for ASCT outpatient management in MM patients?

The most representative models of ASCT as an outpatient procedure are summarized in Figures 1 and 2. There are only a few data to estimate the real impact of outpatient ASCT procedures in western countries. The GITMO survey suggested that this practice was still limited to few centers in Italy. Of the 55 centers who filled out the survey questionnaire, only 6 had implemented an outpatient ASCT program, which overall included 536 procedures out of a total of 1036 ASCT performed between 1998 and 2012. A single-center survey from Mayo Clinics²⁰ suggested that 39% of 716 MM patients completed the transplant procedure as outpatients. Another retrospective series was reported by Holbro et al.,²² who performed 90 outpatient ASCT with very low TRM though 68% of patients required a hospital stay longer than 7 days. Most representative clinical trials of ASCT in MM as an outpatient procedure are summarized in Tables 2 and 3.

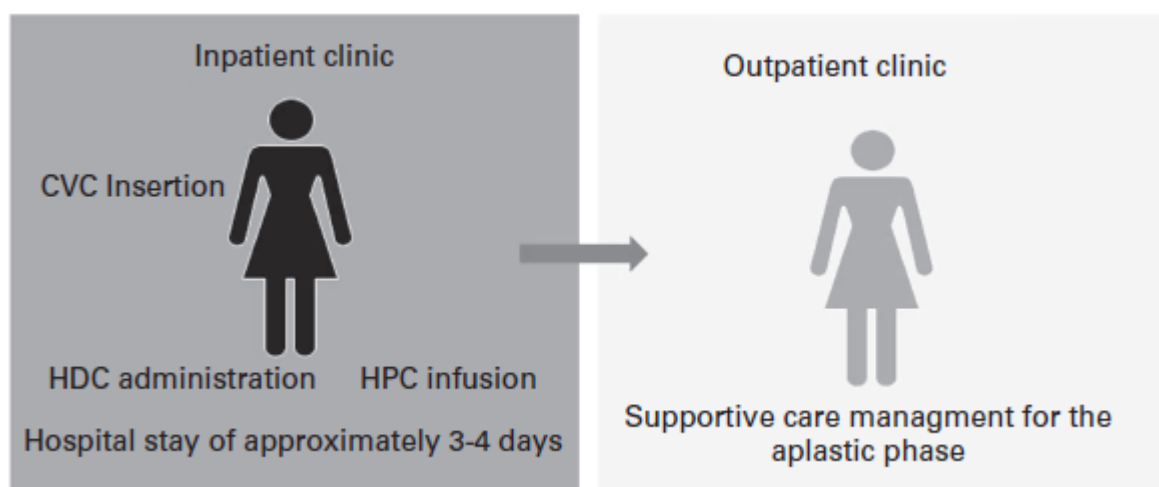


Figure 1. Autologous stem cell transplantation for multiple myeloma through an early-discharge outpatient model. In-hospital admission for conditioning and HPC infusion with discharge on day one post-infusion. Homestay during the aplastic phase with a caregiver (about 10 days) during which twice a week ambulatory visits are scheduled to deliver supportive care if required. HPC=hemopoietic progenitor cell.

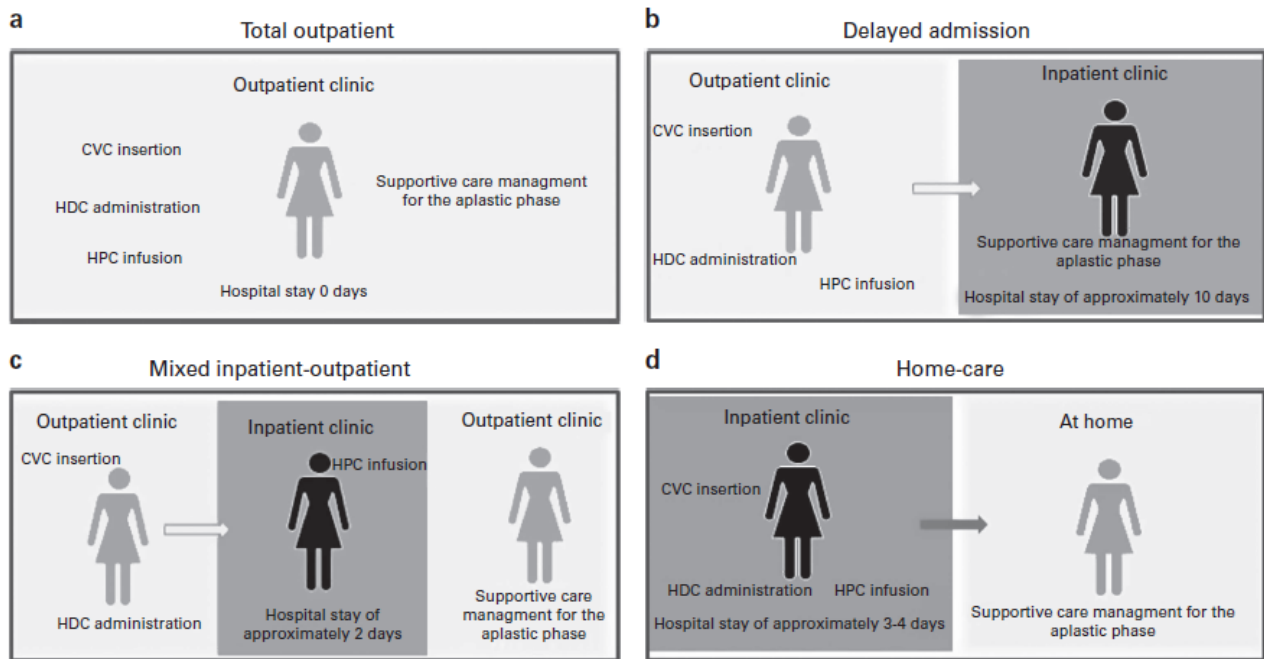


Figure 2. Autologous stem cell transplantation for multiple myeloma through a total, delayed admission, mixed inpatient-outpatient and home-care outpatient model. (a) HDC and HPC infusion are performed as outpatients. After HPC infusion, patients are followed daily on the outpatient service where they receive supportive care. (b) Outpatient clinic for CVC insertion, HDC administration and HSC infusion. Re-admission is scheduled on day 5. (c) CVC insertion, fluid infusion, HDC, as well as supportive care during the aplastic phase are carried out on the outpatient service. Patients are admitted for HPC infusion. (d) In-hospital admission for conditioning and HPC infusion with discharge on day 1 post infusion. The program provided clinical examination performed twice daily (in the morning and the afternoon), daily physician oversight of all evaluations, daily registered-nurse evaluations in the patients' home. CVC=central venous catheter; HDC=high-dose chemotherapy; HPC=hemopoietic progenitor cell.

The panel agreed that differences in ASCT outpatient models and their clinical outcomes in MM might heavily rely on local conditions. However, the panel agreed to recommend the most frequently implemented model reported in the GITMO survey, which is the 'early-discharge outpatient model' (EDOM) that allowed a very low re-admission rate²⁶ (Figure 1). Two additional issues that influence outpatient ASCT models are the cost-effectiveness and quality of life. Various issues must be considered in economics studies, including medical and non-medical direct costs, indirect costs, pre-transplant and post-transplant costs.

A randomized study compared outpatient ASCT with standard inpatient ASCT in 131 patients with non-leukemic malignant diseases and showed that the early-discharge model allowed discharge on day 0, home stay with a caregiver and outpatient follow-up with, however, a re-admission rate of 86%.²¹ In this study, HDM was used as conditioning in only 30% of the patients, and the study population was extremely heterogeneous.

The panel agreed that a cost analysis in this setting required prospective studies. Last, there are not prospective studies comparing the quality of life (QOL) in MM patients treated with outpatient ASCT models. Therefore, the panel agreed that strong recommendations in this setting cannot be established.

Operative questions

How to select MM patients for outpatient ASCT

General recommendations

The expert panel agreed that some specific conditions led to define different inclusion/exclusion criteria from those currently accepted for conventional inpatient ASCT. Moreover, very few data on the outpatient ASCT management of MM patients with impaired renal function or other comorbidities are reported.^{49, 50}

The expert panel selected a list of major criteria to enroll patients in an outpatient ASCT program. A set of specific questions was answered by each panel members and the results with the final list of inclusion/exclusion criteria are reported in the Supplementary File. The panel agreed that advanced age (greater than or equal to 65 years), poor performance status or presence of relevant comorbidities were exclusion criteria.²⁹ The risk of infections should also be carefully evaluated. Local epidemiology, infectious history and colonization status by MDR pathogens require a proper risk assessment for post-transplant infections.

Pre-transplant infections

A history of any severe infection before transplant and the persistence of any microbiological or clinical findings that indicate an incomplete resolution of an infection should be considered a contraindication to outpatient ASCT. Though completely resolved, a history of severe infections by Gram-negative MDR pathogens during the prior 3 months is a contraindication to outpatient ASCT.

Pre-transplant infectious screening

Chest X-ray (or CT scan in selected cases) and additional tests, as clinically indicated, should be performed before transplant. In patients without documented colonization by Gram-negative MDR pathogens, a rectal swab culture should be performed before transplant. When EDOM is planned, colonization monitoring should be started before discharge if a Gram-negative MDR pathogen infection (or colonization) is documented on the hospital ward. Colonization screening should focus on the search of extended spectrum beta-lactamases producer and carbapenem-resistant enterobacteria, and of other Gram-negative MDR pathogens (that is, *Pseudomonas aeruginosa*, *Acinetobacter* spp, *Stenotrophomonas maltophilia*). Colonization by carbapenem-resistant and Gram-negative MDR pathogens is a contraindication to outpatient ASCT given the crucial role played by timely MDR-targeted empiric antibiotic therapy in carriers of MDR bacterial infections.^{51, 52} Colonization by extended spectrum beta-lactamases producing Enterobacteriaceae do not represent an absolute contraindication, but should be taken into account if empiric antibacterial therapy is required during NF (see below).

Inclusion criteria

The expert panel recommended the following inclusion criteria: (1) age between 18 and 65 years; (2) normal cardiac and lung function as usually performed before a conventional ASCT; (3) absence of other relevant organ dysfunctions. Liver impairment, defined as total bilirubin >3 mg/dL, or renal impairment, defined as a creatinine clearance <60 ml/min; (4) absence of advanced disease (for example, <PR); (5) absence of Gram-negative MDR pathogens colonization or infection during the prior 3 months from ASCT. Any severe infection not completely microbiologically or clinically resolved is considered a contraindication to outpatient ASCT; (6) place of stay within 1 h drive from the hospital; (7) availability of a suitable caregiver 24 h/24 h; (7) a dedicated phone line 24 h/24 h at each transplant center to allow patients or their caregivers to contact an expert physician on the transplant team; (8) informed consent including a detailed SOP for the caregiver and the outpatient management.

Which supportive therapy for outpatient ASCT?

Supportive care

Supportive care should not differ from that recommended for conventional ASCT. It should include hydration, management of emesis and metabolic disorders, analgesic therapy and transfusion of blood products. All these treatments can routinely be performed in outpatient rooms except for severe medical conditions requiring hospitalization (see below). Patients with severe mucositis (>grade 2 WHO), unable to drink and requiring continuous treatment with major analgesic drugs should rapidly be re-admitted.

The expert panel agreed that supportive therapies may vary in the light of the different outpatient ASCT models. Two outpatient ASCT models are employed in the GITMO network: the EDOM and delayed admission model (DAM).⁵³ In the EDOM model,^{10, 23, 26} the most commonly used in Italy, patients and caregivers should carefully trained on home behavior and a detailed information sheet on the management of mild/moderate mucositis, fever or mucosal bleeding should be provided for the general practitioner. In the delayed admission model, discharge is scheduled on day 1 and re-admission on day 5 post-HSC infusion. The results of this approach, however, do not strongly support that the delayed admission model may significantly reduce hospital stay and its costs when compared with the other model.

Antimicrobial prophylaxis

The expert panel agreed that antimicrobial prophylaxis for outpatient ASCT should not differ from that recommended for conventional inpatient ASCT.^{54, 55, 56, 57, 58} Patients should receive antibacterial prophylaxis with ciprofloxacin 500 mg twice daily or levofloxacin 500 mg once a day from day 0 until stable neutrophil engraftment. A recent study suggests that Levofloxacin prophylaxis is associated with decreased risk of bloodstream infection and fever in patients with myeloma undergoing ASCT.⁵⁹

Primary antifungal prophylaxis is not recommended in the ASCT setting.^{60, 61} However, in the case of symptomatic mucositis, oral fluconazole at 200–400 mg/day should be started until complete hematological recovery. Even though the full resolution may have occurred, secondary

antifungal prophylaxis in patients with previous invasive fungal infections is recommended. Antiviral prophylaxis from the day -2 until neutrophil engraftment for up to 3 months post transplantation or longer at the discretion of the attending physician is recommended. Pneumocystis jiroveci prophylaxis is recommended after engraftment and for 3 months post transplant or until a satisfactory immunological recovery (CD4+ lymphocytes cells >200/mm³).

Infection monitoring

After discharge, the first follow-up visit should be recommended at day +5 and then scheduled twice weekly until sustained hematological recovery. Patients and caregivers and family members should be properly trained on careful monitoring of fever and other infectious signs/symptoms. Surveillance blood cultures in the absence of fever or other infection signs are not required regardless of the presence of a central venous catheter. Finally, surveillance for fungal infections with biomarkers (that is, plasma galactomannan, beta-d-glucan, fungal PCR) is not required.

Management of neutropenic fever

In the event of fever (body temperature >38 °C in two measurements or >38.3 °C as a single measurement) during neutropenia, patients should be evaluated within 1–2 h by an expert hematologist on call who will decide on the need for hospitalization and the choice of the antimicrobial therapy. The expert panel strongly suggests a 24-h active phone line with the hematologist on call in the BMT unit. According to the local policy and based on clinical conditions, the clinical examination may be performed either at home, by the general practitioner or in an emergency department, in case of worrying symptoms and/or a low MASCC score; in both cases, the general practitioner will be able to give an immediate feedback to the hematologist on call and (if needed) to start an oral antibiotic treatment. The expert panel recommends that a detailed standard operative procedure in the case of NF should be available contextually at the time of the informed consent (a dedicated form must be prepared for the outpatient ASCT procedure), not only for the patient but also for the caregiver and the general practitioner. The evaluation of the febrile episode should include a physical exam, at least, two blood cultures and imaging when clinically indicated.

Which re-admission criteria and how to manage ASCT outpatients with significant complications?

Re-admission criteria should include: (a) severe mucositis (with/without fever) unresponsive to outpatient management; (b) fever with grade greater than or equal to 2 mucositis; (c) fever >38.3 °C should be evaluated within 1–2 h from onset by an expert hematologist (at least by phone, see paragraph ‘Management of NF’). Overall, in patients with a–b–c blood pressure, O₂ saturation and vital signs should carefully be monitored. After at least 6 h monitoring, hemodynamically stable patients without relevant clinical problems may be followed as outpatients.

The expert panel agreed on the potential usefulness of the MASCC score,⁶² although this index has not been validated in the ASCT setting. An MASCC score as low as 21 or lower (high-risk patients) was considered a criterion for rapid re-admission through a score higher than 21 was not considered a sufficient criteria per se to define patient at low risk and delay re-admission. In case of NF the panel agreed on the following re-admission criteria:

- Hemodynamic instability (for example, tachycardia and low blood pressure), impaired respiratory function (increased respiratory frequency and low oximetry on room air), oliguria, altered mental status and other signs of clinical instability.
- Grade >2 oral mucositis and diarrhea.
- Colonization by extended spectrum beta-lactamases producing Enterobacteriaceae (colonization by other MDR pathogens).
- Fever persisting after 2 days of broad spectrum antibacterial therapy.
- Low compliance of the patient.

The use of empiric antibacterial therapy should follow guidelines/recommendations for patients with hematologic malignancies and NF. Empiric broad-spectrum antibacterial therapy should be initiated within 1 h from clinical evaluation and after blood cultures have been obtained, and fever workup has been completed. IV antibiotics should be preferred and chosen in the light of clinical and laboratory findings. Outpatient oral antibiotic therapy (that is, amoxicillin-clavulanate) in low-risk patients may be considered.

How to optimize the performance of ASCT outpatients?

The expert panel also addressed three potentially relevant issues which may be critical to improving the performance of the outpatients ASCT model:

- Re-hospitalization;
- NF incidence;
- QOL.

Re-hospitalization for outpatients is most commonly due to severe oral mucositis (grade 3–4 WHO) which requires TPN and narcotic analgesics; NF unresponsive to oral antibiotics which impairs PS or determines hemodynamic instability; psychological distress or loss of caregiver support.

Decreased incidence of mucositis in patients transplanted as outpatients is of pivotal importance given that mucosal damage increases the risk of many complications that may easily cause re-admission. Palifermin administered pre- and post-HDM was studied in a randomized fashion with no beneficial effect on mucositis incidence and on fever.⁶³ Other studies, however, found a positive impact of palifermin on infection rate after BEAM-like conditionings or after TBI.^{64, 65, 66} Furthermore, some studies suggested that, though palifermin was not effective in reducing overall infection rate (mostly central venous catheter related), its use may reduce ‘severe’ infections such as those due to Gram-negative pathogens or accompanied by focal pneumonia.^{66, 67}

In many centers, G-CSF administration is not routinely performed when the source of hematopoietic cells is mobilized peripheral blood, and the dose of CD34+ cells infused is largely above the threshold required for a proper engraftment. When a CD34+ cell dose $>5 \times 10^6/\text{kg}$ is employed, neutropenia is unlikely to be further shortened by the administration of post-transplant G-CSF. Filgrastim and lenograstim are the standard G-CSF molecules used for enhancing neutrophil recovery after ASCT. Very few data on the use of biosimilar G-CSFs have been reported so far^{68, 69} though they have successfully been used for HSC mobilization.⁶⁹ PEGylated G-CSF was also used^{70, 71} and, in the GITMO survey, many patients on outpatient ASCT programs were given PEG-G-CSF.²⁶

The issue about the global economics involved in the outpatient ASCT procedure is still debated. However, several experiences suggest that this approach could induce a significant sparing of the direct costs, due to the reduced number of hospitalization in intensive care unit.^{23, 24}

Conclusions

Notwithstanding its appeal, outpatient ASCT in MM has not yet been established as a routine procedure, and many transplant centers are reluctant to adopt this approach. However, the extensive use of some outpatient ASCT models in MM may contribute to making ASCT more competitive especially when compared with some expensive new drugs. Among the different approaches, the mixed inpatient/outpatient model was shown to be highly feasible with a very low re-hospitalization rate and without increased TRM. One of the reasons for its low implementation may be the lack of specific reference recommendations/guidelines. The present consensus may represent a valid tool to widen this policy to both Italian and European transplant centers.

Notes

Author contributions

Each member of the panel was assigned a specific topic and proposed recommendations during the meetings. All authors discussed the final version in a plenary session. MMA, RML and AO drafted the final report which was, in turn, reviewed and approved by the whole panel.

Conflict of interest

The authors declare no conflict of interest.

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